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Review

Non-coding RNAs in DNA damage and repair

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ABSTRACT

Non-coding RNAs (ncRNAs) are increasingly recognized as central players in diverse biological processes. Upon DNA damage, the DNA damage response (DDR) elicits a complex signaling cascade, which includes the induction of multiple ncRNA species. Recent studies indicate that DNA-damage induced ncRNAs contribute to regulation of cell cycle, apoptosis and DNA repair, and thus play a key role in maintaining genome stability. This review summarizes the emerging role of ncRNAs in DNA damage and repair.

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1. Introduction

1.1. DNA damage and repair

Genomes continually face the challenge of DNA damage caused by environmental and endogenous insults. To combat the potential adverse effects from DNA damage cells have developed a sophisticated signaling cascade to sense and repair DNA damage and maintain genome integrity. Depending on the source of damage, DNA may experience a wide variety of lesions such as modification of bases, single strand breaks (SSBs), or double strand breaks (DSBs) [1,2].

Repair of DNA lesions by the DDR pathway comprises three major steps: (i) detection of damage by sensors, (ii) recruitment of repair factors to sites of damage by signal transducers and (iii) repair by effectors [3]. Repair of different types of DNA damage is carried out by specific repair pathways: DNA mismatches are corrected by mismatch repair (MMR), whereas chemical modifications of DNA bases are repaired by base excision repair (BER) [4,5]; the nucleotide excision repair (NER) pathway corrects more complex lesions such as pyrimidine dimers and intrastrand crosslinks [6,7], and SSBs are repaired by single-strand break repair (SSBR) [8]; DSBs, which are the most toxic and difficult to repair DNA lesions, are corrected either by non-homologous end joining (NHEJ) or homologous recombination (HR). NHEJ occurs primarily during pre-replicative (G0 and G1) phases of the cell cycle and does not require a template DNA sequence since broken DNA ends are directly rejoined. On the other hand, HR requires a homologous DNA template sequence for error-free repair and predominates in S phase of the cell cycle. For repair of DSBs by HR, DNA ends are resected to yield 3′ single-strand DNA overhangs and the resected DNA, with help of HR proteins, permits strand invasion of a partner homologous sequence to form a nascent D-loop structure [9]. This is followed by synthesis of DNA by the synthesis-dependent strand annealing (SDSA) pathway or the double-strand break repair (DSBR) pathway [9]. Repair of DSBs is mediated by proteins of the phosphatidylinositol 3-kinase-like protein kinase (PIKKs) family, particularly ATM, ATR, and DNA-PKcs, and the choice of repair pathway is influenced by type of lesion and the cell cycle phase [10]. In NHEJ, DSBs are recognized by Ku70–Ku80 heterodimers leading to activation of DNAPKcs, which then stabilize DSBs through phosphorylation of the repair protein Artemis, the histone variant H2AX, and by recruitment of XRCC4/LIG4 ligase complex for religation of the broken ends with the help of the stimulatory factor XLF [7]. For repair by HR in S-phase, DSBs are detected by the MRE11-RAD50-NBS1 (MRN) complex, which promotes the activation of ATM by autophosphorylation [11]. This is followed by the rapid phosphorylation by ATM of various DNA repair factors such as H2AX, CtIP, BRCA1 and exonuclease EXO1 [9].DDR activation leads to phosphorylation of histone H2AX (γH2AX), which is

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bound by mediator protein MDC1 with high affinity. MDC1 in turn triggers the recruitment of chromatin remodeling- and modification-complexes, which allow the association of downstream factors, such as 53BP1 and BRCA1. 53BP1 is an inhibitor of BRCA1 accumulation at DSB sites in the G1 phase of the cell cycle and promotes NHEJ, whereas BRCA1 promotes end resection and HR [12–14]. Single-stranded DNA generated by resection due to the activities of MRE11, CtIP, EXO-1 and BRCA 1, is rapidly coated by replication protein A (RPA) and is subsequently replaced by RAD51 in the presence of BRCA2 [9]. The single-strand ends bound by repair proteins can subsequently invade the homologous template to prime DNA synthesis, which copies and restores genetic information disrupted by the DSB. Although ATM is the primary responder to DSBs in S-phase, recent evidence suggests that ATR, which responds to ssDNA and stalled replication forks, is also activated upon ionizing radiation (IR)-induced DSBs in a cell-cycle dependent manner. ATR activation in response to DSB occurs during S- and G2-phase of the cell cycle and requires ATM, MRN and CtIP [15,16].

In response to damage and activation of the DDR, cells may undergo cell cycle arrest until repair is complete or, if the damage is irreparable, cells undergo apoptosis or move into senescence. While the primary response to DNA damage is very fast and mediated through posttranslational modifications, such as phosphorylation by kinases of the PIKKs family, the decision to induce cell-cycle arrest or apoptosis is mediated through the slower transcriptional responses largely mediated by p53, which is regulated by ATM and CHK2 in response to DSBs [17]. Following DSBs, p53 is activated by the ATM kinase through a transcriptional circuit involving the WIP1 phosphatase and the MDM2 E3 ubiquitin ligase, which are induced by p53 and negatively regulate ATM and p53, respectively [18].

The DNA repair process manifests itself in the form of stable cytological structures called DNA-repair foci, generated by recruitment and accumulation of DNA-repair factors at the site of DNA damage [19,20]. These foci are intrinsically dynamic in nature and are formed by the continuous exchange of DNA-repair factors between the chromatin-bound pool and the freely diffusing nucleoplasmic pool at the site of DSBs [19,20]. Details of the structural organization of repair foci have not been elucidated, but some of the factors involved in the formation of foci are the sensor complex MRN, the DDR mediator MDC1, ATM kinase and the downstream factors γ-H2AX, 53BP1 and BRCA1. It is not known whether the accumulation of repair factors in foci is essential for efficient repair or is merely a byproduct of the repair process, but it is possible that they play a key role in the repair process by concentrating essential factors and/or by keeping the broken ends in spatial proximity, enhancing the efficiency of repair [19]. Chromatin modifications and remodeling events, most prominently the phosphorylation of H2AX, around the DNA lesions are thought to contribute to the fine-tuning of damage signaling and repair [19,21–23]. In order to facilitate repair and checkpoint signaling, chromatin undergoes rapid local and global decondensation in response to DNA damage [24,25]. Apart from phosphorylation of the C-terminal tail of H2AX, several modifications of multiple core histones through acetylation, methylation, ubiquitination and phosphorylation, have been linked to various aspects of DNA damage and repair [19,22,26].

1.2. Non-coding RNAs (ncRNAs)

During the last decade our understanding of genome organization has significantly increased and it has been recognized that large stretches of once assumed non-transcribed intergenic regions in fact code for a large number of non-coding transcripts [27–30]. Non-coding RNAs are generally defined as RNA species that do not have protein coding potential. With the exception of ncRNAs such as ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), and transfer RNAs (tRNAs), the remaining ncRNAs are arbitrarily grouped into short (<200 nt) and long (>200 nt) ncRNAs. Short RNAs can be further subdivided into microRNAs (miRNAs), piwi interacting RNAs (piRNAs) and small interfering RNAs (siRNAs). Short and long ncRNAs differ in their origin, processing and mode of action. Increasing evidence suggests that various ncRNAs play a pivotal role in DDR. This was not unexpected, as changes in transcription and chromatin structure that are an integral part of DDR are also modulated by ncRNAs [31–33]. This review highlights the emerging roles of ncRNAs in DDR.

1.3. miRNAs

miRNAs are short (~19–24 nt), single-stranded ncRNAs that regulate gene expression at the post-transcriptional level either by cleavage of target mRNA or by repressing translation [34,35]. miRNAs probably contribute to the regulation of most major gene pathways as more than half of the human transcriptome is predicted to be under miRNA regulation [36,37]. miRNAs biogenesis and maturation is a complex multi-step process and initiates with their transcription by RNA polymerase II into primary miRNA (pri-miRNAs) from intergenic or intronic/exonic loci, often during transcription of their host genes. The pri-miRNAs are then cleaved in the nucleus by the DROSHA-DGCR8 microprocessor to generate approximately 70-nt long hairpin-shaped precursors called pre-miRNAs [38]. The transport of pre-miRNAs from the nucleus to the cytoplasm is mediated by exportin-5, a RanGTP-binding nuclear transporter [39,40]. In the cytoplasm, the RNAse III-like enzyme DICER and TARBP2 (TAR binding protein 2) cleaves pre-miRNAs into a transient duplex of around 20–24 nt in size made up of the functional miRNA strand and the passenger strand [39,40]. The mature miRNA binds to Argonaute (Ago) proteins to form an miRNA-induced silencing complex termed RISC, which mediates gene silencing by mRNA degradation or translation inhibition [41,42]. Target recognition by miRNA generally depends on base-pairing between miRNA seed sequence (nt 2–8 at the 5′ end of miRNA) and sequences in the 3′ UTR of the target mRNA. The choice of gene silencing by mRNA degradation or translation inhibition appears to be determined by degree and nature of complementary sites between miRNA and the mRNA target [37,43–45]. Interestingly, it has been recently shown that translational inhibition precedes mRNA degradation and is necessary for mRNA degradation by miRNAs [46]. Expression and biogenesis of several miRNAs is affected by DNA damage whereas, in turn, some miRNAs regulate DNA repair factors (Fig. 1).

1.4. Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are defined as RNA species longer than 200 nt that do not appear to have protein coding potential [33]. Use of tiling arrays has revealed that a vast majority of the genome is transcribed and that transcription is not limited to protein-coding regions, but is instead pervasive and the genome probably codes for as many, if not more, lncRNAs genes as protein coding genes [47–50]. lncRNAs have been shown to play functional roles in numerous biological processes ranging from cell cycle control and pluripotency, to differentiation and disease. They can act as both *cis*- and *trans*-regulators of gene activity and as modulators of the epigenome [33,51–53]. lncRNAs have been classified on the basis of their position with respect to protein coding genes: (i) antisense lncRNAs arise from the antisense strand of known protein-coding genes, (ii) intronic lncRNAs are encoded within introns of protein-coding genes, (iii) long intergenic non-coding RNAs (lincRNAs) are transcribed from intergenic regions between protein coding genes, and (iv) bidirectional lncRNAs that initiate in the

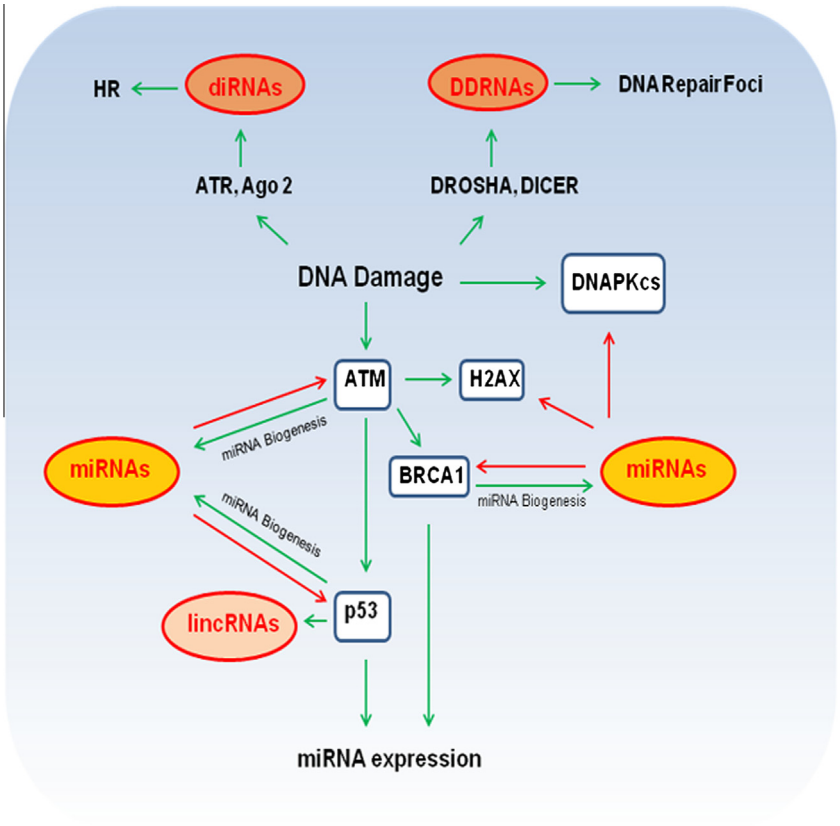

Fig. 1. The complex interplay of ncRNAs and DNA damage. Activation of the DNA damage response (DDR) induces multiple kinds of non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), DROSHA- and DICER-dependent (ddRNAs), DSB-induced small RNAS (diRNAs), and long intergenic non-coding RNAs (lincRNAs). ATM, BRCA1 and p53 are involved in regulation of miRNA biogenesis. P53 and BRCA1 also regulate miRNA expression. Misregulated miRNAs expression such as in cancer may contribute to direct inhibition of key proteins in DDR such as ATM, DNAPKcs, H2AX, BRCA1 and p53. DDRNAs produced from sites of DNA damage contribute to formation of DNA repair foci. diRNAs contribute to HR mediated repair. p53 also induces expression of lincRNAs which modulate gene expression to regulate cell cycle and apoptosis. Activating effects (green), inhibitory effects (red).

opposite direction from the promoter of a protein coding gene [33]. The molecular mechanisms by which lncRNAs exert their function is not fully understood, but emerging studies indicate that lncRNAs associate with proteins in chromatin or ribonucleoprotein complexes and act as signals, decoys, guides or scaffolds for these protein complexes to execute their activities in the genome [33,54]. Some examples of lncRNA expression in response to DNA damage have recently emerged (Fig. 1), and will be discussed below.

2. miRNAs in DNA damage

2.1. miRNA expression upon DNA damage

A role for miRNAs in the cellular response to DNA damage is supported by the fact that knock-down of key miRNA processing proteins, particularly DICER or Ago2, reduces survival and checkpoint response after UV damage and is accompanied by cell-cycle-dependent relocalization of Ago2 into cellular stress granules [55]. In addition, a large number of miRNAs are transcriptionally induced upon DNA damage and the level of induction is variable depending on cell type and the nature and intensity of DNA damage [55–63].

The transcription of a subset of miRNAs in the DDR is dependent on the tumor suppressor p53, a well-studied transcription factor that is activated upon DNA damage and induces growth arrest or apoptosis. The study of miRNA expression profiles in wild-type and p53 null cells revealed that expression of three miRNAs, miRNA-34a, miRNA-34b and miRNA-34c, is precisely correlated with p53 status [64]. Overexpression of miRNA-34a induces apoptosis and G1 arrest [64–66]. miRNA-34c overexpression suppresses c-Myc expression and is thought to prevent inappropriate replication which may promote genomic instability [67]. Induction of miR-34c also occurs independently of p53 via the alternative ATM-dependent p38MAPK signaling pathway [67]. Apart from the miR-34 family, a p53-dependent upregulation of miRNA-192, miRNA-194 and miRNA-215 upon genotoxic stress also induces cell cycle arrest [68–71]. Conversely, p53-mediated transcriptional repression of miRNAs has also been reported. In cells subjected to hypoxia, levels of the miRNA-17–92 cluster were reduced in cells containing wild-type p53, but were unchanged in p53-deficient cells [72] and overexpression of the miRNA-17–92 cluster inhibits hypoxia-induced apoptosis [72]. Upon irradiation, a decrease in expression of the let-7a and let-7b family of miRNAs is observed in human and mice cells [73]. This decrease in expression of let-7a and let-7b miRNAs is dependent on p53 and ATM [73]. These studies suggest that regulation of miRNA expression by p53 modulates the cellular response to DNA damage via regulation of cell cycle checkpoints and apoptosis. In fact, promoters of a number of components of the miRNA processing machinery, including Dicer, contain p53 response elements, suggesting that they could be direct transcriptional targets of p53 [74]. P53-induced miRNAs also play regulatory roles in other cancer-associated processes such as tumorigenesis, metastasis, epithelial-mesenchymal transition and metabolic adaptation [75,76]. However, it is currently not clear whether p53-induced miRNAs actually control any genes directly involved in DNA repair. Multiple physiological stress conditions

such as oncogenic stress can activate p53-mediated transcriptional programs, but miRNA expression profiles in response to direct activation of p53 by DNA damage have not been studied in detail. More studies are required to specifically identify miRNAs induced by direct p53 activation upon DNA damage andto elucidate the role of these miRNAs in regulating proteins important in DDR. In addition to p53, other proteins in the DNA repair pathway also regulate miRNA expression. Besides its role in miRNA biogenesis, *BRCA1* represses transcription of miRNA-155 [77]. *BRCA1* epigenetically represses miRNA-155 expression via its association with the histone deacetylase HDAC2, which in turn deacetylates histones H2A and H3 on the miR-155 promoter [77].

2.2. Regulation of miRNA biogenesis by DDR factors

The key DNA repair factors ATM and BRCA1 have been shown to modulate miRNA biogenesis by phosphorylating and interacting with components of the DROSHA microprocessor complex [78,79]. About 25% of the miRNAs induced upon DNA damage depend on ATM for upregulation [79] and ATM specifically regulates processing and biogenesis of these miRNAs by phosphorylating splicing-regulatory protein KSRP without affecting their transcription. KSRP is a component of both the DROSHA and DICER complexes and has been previously shown to promote biogenesis of a subset of miRNAs [80]. KSRP phosphorylation by ATM leads to enhanced interaction between KSRP and terminal loops of pri-miRNAs which in turn allows for increased recruitment of these pri-miRNAs for processing by DROSHA and DICER[81].

BRCA1 also regulates miRNA biogenesis (Fig. 1). However, unlike ATM, BRCA1 directly binds to both specific pri-miRNAs and DROSHA [78]. *BRCA1* binds to specific pri-miRNAs via its DNA-binding domain due to its ability to recognize a stem-loop in the secondary structure of pri-miRNAs [78]. More studies are required to understand how regulation of miRNA biogenesis by ATM and *BRCA1* contributes to maintenance of genomic stability.

p53 also facilitates the processing of specific pri-miRNAs into pre-miRNAs independently of transcription by associating with DDX5, a component of the DROSHA-DGCR8 microprocessor complex [82]. This association leads to an increase in the levels of the mature miRNAs, such as miR-16–1, miR-143 and miR-145 [82]. Use of computational approaches to identify molecules that regulate miRNA processing also suggest that p53 and its related family members p63 and p73 regulate components of miRNA processing [74].

2.3. miRNA regulation of proteins involved in DDR

While some DDR proteins appear to regulate miRNA expression, miRNAs in turn also influence DDR protein expression (Fig. 1). Key DNA repair proteins such as ATM, H2AX and BRCA1 are subjected to direct inhibition by miRNAs. ATM is targeted by miRNA-421, miRNA-18a, miRNA 26b, miRNA-101, miRNA-181 and miRNA100 [83–88]. miRNA-421 suppresses ATM expression by targeting the 3′ UTR of the ATM transcript [83]. Ectopic expression of miR-421 in cells results in increased sensitivity to IR [83,89] and overexpression of other miRNAs that target ATM also reduces ATM expression, alters cell cycle checkpoints, and leads to hypersensitivity to IR. Interestingly, apart from ATM, miRNA-101 also inhibits DNA-PKcs via binding to the 3′-UTR of DNA-PKcs transcripts [87]. These observations suggest a feedback loop between miRNAs and ATM (Fig. 1).

H2AX, which plays a key role in DNA damage signaling via phosphorylation of its C-terminus, is a target of miRNA-24 [90]. Up-regulation of miRNA-24 in post-replicative cells reduces H2AX and thereby renders cells highly vulnerable to DNA damage [90]. Screening of a library of human miRNA-mimics in osteosarcoma cells revealed several miRNAs that inhibit γH2AX foci formation [91]. Among them, miR-138 was shown to directly target the histone H2AX 3′-untranslated region, to reduce histone H2AX expression, and to induce chromosomal instability after DNA damage [91].

BRCA1 is an important player in homologous recombination and also regulates miRNA processing. *BRCA1* is a target of miRNA-182 [92]. Down regulation of miRNA-182 increases BRCA1 protein levels and protects cells from IR-induced cell death [92]. Consistent with this, overexpression of miRNA-182 reduces BRCA1 protein levels, impairs homologous recombination-mediated repair, and renders cells hypersensitive to IR [92]. Pull-down experiments with synthetic miRNA indicate that apart from *BRCA1*, miRNA-182 also targets a set of other genes involved in the DDR pathway [93]. Interestingly, miRNA-96, which is expressed as a polycistronic transcript with miRNA-182, targets RAD51, which, together with *BRCA1*, is involved in homologous recombination [94]. miRNA-146a and miRNA-146–5p bind to the same site in the 3′UTR of *BRCA1* and down-regulate its expression [95]. In breast tumors, levels of these miRNAs are inversely correlated with that of the BRCA1 protein and these miRNAs are overexpressed in triple negative breast cancers, the most common type of breast cancer in women with BRCA1 mutations [95]. miRNA-1, a candidate prognostic marker of prostate cancer and miRNA-1245, a c-myc induced miRNA, also regulate DNA repair by targeting BRCA-1 and BRCA-2, respectively [96,97]. Interestingly, it has been shown that overexpression of miR-99a and miR-100, which target SNF2H, a SWI/SNF chromatin remodeling factor, leads to reduced localization of BRCA1 and RAD51 to sites of DNA damage [98], suggesting that miRNA regulation occurs at many steps in the DNA repair and signaling cascade.

Several miRNAs including miR-125b, miR-504, miR-33, miR-380–5p, miR-1285, miR-30d and miR-25 have also been shown to downregulate p53 in a context-dependent manner [99–104]. Ectopic expression of these miRNAs induced phenotypes that are associated with the loss of p53.

CU1276 is a miRNA derived from tRNA which was first identified during screening of miRNA expression in human B cells [105,106]. CU1276 is derived from tRNA, by DICER dependent biogenesis and associates with Ago proteins, and represses in a sequence-specific manner transcripts of RPA1, which is a key gene in DNA replication and repair [106].

Finally, using computational approaches miRNA binding sites have been found in several DSB sensors with long 3′ UTRs such as NBS1 and Ku80, and they have been predicted to be regulated by miRNAs, but these predictions have not yet been validated experimentally [107,108].

3. Non-canonical small RNAs in DNA damage response

DNA damage also induces DROSHA- and DICER-dependent small RNAs called DDRNAs (Fig. 1), which are distinct from the canonical miRNAs [109]. These transcripts are produced from sequences transcribed from the damaged site and control DDR foci formation in cultured human and mouse cells and in zebrafish [109]. In support of an active role of DDRNAs inDDR, transient inactivation of DICER or DROSHA in human cells exposed to IR impaired formation of pATM-, 53BP1-, and MDC1-foci, but not γ-H2AX foci, without decreasing the level of these proteins, suggesting that DICER and DROSHA RNA products control DDR activation and act independently from canonical miRNA-mediated repression of DDR factors [109]. Moreover, RNase A treatment reduces repair factor foci formation in DNA damaged cells [109]. Interestingly, it has been shown that 53BP1 associates with RNA and that RNase A treatment dissociates 53BP1 from IR-induced foci [110]. Further-

more, RNase A inhibition or addition of exogenous total RNA purified from the same cells, but not tRNA, can rapidly restore DDR foci formation in DNA damaged cells treated with RNase A [109]. Restoration of DDR foci upon RNase A inhibition in RNase-treated cells is prevented by α-amanitin, suggesting that DDR foci stability requires RNA polymerase II-dependent transcription [109]. Use of a site-specific chromosomally integrated DNA damage reporter system [111] and deep sequencing indicates that DDRNAs originate from the damaged genomic locus [109].

The production of small RNA species from near the site of DSB has also been described in *Arabidopsis thaliana* and these RNAs have been termed DSB-induced small RNAs (diRNAs) (Fig. 1) [112]. These diRNAs require the PI3 kinase ATR, RNA polymerase IV, and DICER-like (DCL) proteins for their biogenesis and they are recruited by AGO2 to mediate DSB repair [112]. Interestingly, while diRNAs were generated from sites in the immediate vicinity of the DNA break in *Arabidopsis*, deep sequencing in human cells revealed that diRNAs are generated from sense- and antisense-strands within a 5 kb region of the damage site [112]. These diRNAs appear to regulate HR mediated repair of DSBs in *Arabidopsis* and humans [112].

Induction of small RNAs upon DNA damage seems to be conserved across species, such as the production small RNAs termed qiRNAs, from the rDNA locus in response to DNA damage in the fungus *Neurospora crassa*[113]. The exact function of these qiRNAs is unclear but *Neurospora* strains with mutations in any proteins involved in qiRNA biogenesis show heightened sensitivity to DNA damage [113]. In *Drosophila*, analogous to DDRNAs and diRNAs, transfection of linearised plasmid DNA mimicking DSB ends elicits induction of small RNAs known as endo-siRNAs [114]. This response is specific to DSBs, depends on *Drosophila* endo-siRNA factors such as Dcr-2, and has the capacity to silence transcripts with homologous sequence *in trans*[114].

Chowdhury et al. have speculated on the possible roles these small ncRNAs could serve in DNA repair. They suggest that they may act (i) as a template for DNA polymerase to fill in for resected DNA in HR, (ii) as guides for recruiting DNA repair factors or chromatin modifying complexes at DSBs, (iii) in siRNA pathways to degrade nascent RNA from the damaged loci to prevent its aberrant expression or (iv) the ncRNA and Ago complex may act as scaffold for maintaining repair foci [107]. Overall these studies suggest that small RNAs generated from the site of DSB or the regions flanking a DSB are important for DSB repair. The precise mechanisms of action and function of these ncRNAs remain unclear, additional studies dissecting the exact molecular and biochemical function of these unique classes of small RNAs are required.

4. Long non-coding RNA in response to genotoxic stress

The first indication that lncRNAs are induced in response to DNA damage was the identification of non-coding, >200 nt, low copy number, pol II-regulated, polyadenylated, uncapped transcripts generated upstream of the *CCND1* promoter in response to DNA damage [115]. These transcripts were shown to bind to TLS, an RNA-binding protein that has been suggested to play roles in DNA repair and is an inhibitor of histone acetyl transferase CBP/p300 [115,116]. Upon upregulation by DNA damage, these ncRNAs bind to TLS to activate it and promote its interaction with CBP/p300 to cause repression of *CCND1* transcription, a cell cycle regulator [115].

Subsequently, several p53-dependent lincRNAs induced upon genotoxic stress were identified [117]. One of these, lincRNAp21, has been shown to play an important role in p53-dependent gene repression [117]. LincRNAp21 is located 15 Kb upstream of the gene encoding the cell cycle regulator p21. The p53-dependent transcriptional repression by lincRNA-p21 is mediated through its physical association with the transcription- and RNA processing-factor hnRNP-K. This interaction is required for proper genomic localization of hnRNP-K at p53-repressed genes [117]. Interestingly, another lncRNA TUG1 is also induced by p53, binds to PRC2, and has a role in repressing specific genes involved in cell-cycle regulation [29].

To identify functional ncRNAs in the promoter region of 56 human cell-cycle genes, Hung et al. used high resolution tiling arrays to probe polyadenylated transcripts in response to diverse perturbations including DNA damage [118]. They identified one lncRNA, named *PANDA* (P21 associated ncRNA DNA damage activated), which is induced in a p53-dependent manner. Similar to lincRNAp21, *PANDA* is located 5 kb upstream of the cell cycle regulator p21. *PANDA* interacts with the transcription factor NF-YA to impede induction of pro-apoptotic genes by NF-YA and *PANDA* knockdown sensitizes cells to DNA-damage induced apoptosis [118].

Finally, in response to genotoxic agents such as the DSBs-inducers mitomycin C or the topoisomerase II inhibitor doxorubicin, mammalian cells induce distinct nuclear long ncRNAs [119]. These lncRNAs are not likely to be transcriptional noise as they are ubiquitously expressed in various human tissues. Specific functions for these lncRNAs, however, remain unknown [119].

Given the fact that DNA repair factors like 53BP1, KU80 and *BRCA1* associate with RNA [110,120,121], that certain RNA binding proteins like RBMX and hRNPU are recruited to sites of DSBs [122,123] and that the telomeric repeat-containing RNA TERRA associates with DNA repair proteins [124,125], it is likely that DNA damage-induced lncRNAs play a role in DDR. As of now, information about the function of lncRNAs in DNA damage is only available for lincRNAp21 and *PANDA*. lncRNAs may function in various ways in DDR pathway such as (i) by acting as guides or signals for recruitment of repair proteins or chromatin modifying complexes to sites of DNA damage, (ii) acting as scaffolds for DNA repair proteins or the chromatin remodeling machinery at the site of DNA repair foci, (iii) lncRNA may prevent the action of negative regulators of DNA repair at the site of DNA damage by acting as decoys, or (iv) lncRNAs may act as regulators of DNA damage sensitive gene expression programs like lincRNAp21 and *PANDA*.

5. Conclusions and future perspectives

DNA damage leads to the induction of several ncRNA species (Fig. 1). The majority of studies on ncRNAs in the DNA damage response have so far focused on the role of miRNAs. It is evident that miRNA induction after DNA damage modulates cell cycle progression and alters the sensitivity of cells to DNA damage by targeting downstream gene expression. Since different cell types activate non-overlapping sets of miRNAs upon DNA damage and the miRNA response varies depending on the nature of the DNA damaging agent, it is tempting to speculate that different miRNAs play distinct roles in different repair pathways. The ability of miRNAs to repress key DDR factors has been demonstrated. However, most of these studies have been done in cancer lines and it is not evident how miRNAs contribute to DNA repair in normal cells and whether these responses reflect cancer-specific pathways. It will also be important to examine whether molecules like 53BP1, NBS1 and Ku 80, which have been predicted to have miRNA binding sites, are actually regulated by miRNAs in vivo. Further studies are also required to delineate the role of miRNAs in different repair pathways such as BER and NER. Considering the fact that many miRNAs are late responders in DDR, it is also probable that miRNAs play a role in repressing DDR proteins after completion of repair.

The recent discovery of DDRNAs and diRNAs [109,112] has raised several intriguing questions. To start with, the exact origin of these small RNAs remains unclear. Francia et al. suggest that

they arise directly from the site of DSBs [109] whereas Wei et al. suggest that small RNAs are produced from regions around the DSBs [112]. It remains to be seen what the reason for these differences is. Furthermore, the observed requirement for RNA polymerase II-dependent transcription for DDR foci stability needs to be reconciled with the notion that DNA damage inhibits transcription [126,127]. These observations also raise the important question of whether DNA repair foci formation mechanisms are different in transcriptionally silent heterochromatin regions compared to transcriptionally active euchromatin. It is also not clear whether these non-canonical small ncRNAs are induced by other kinds of DNA damage in addition to DSB. Furthermore, it would be important to study the localization of these small ncRNAs by FISH.

In addition to the miRNAs and other short ncRNAs, numerous lncRNAs have been discovered, which are induced upon DNA damage. However, for most of these lncRNAs there is no experimental evidence available to indicate a functional role in DDR and further studies are required to evaluate their role in DDR. Since it is now believed that a large number of intergenic regions are transcribed into lncRNAs, it is possible that lncRNAs may be the RNA source for DICER and DROSHA processing of short RNAs required for DNA repair upon DNA damage at these loci.

Efforts are still needed to identify and further characterize additional ncRNA species involved in DDR. Use of RNA Immunoprecipitation followed by high-throughput sequencing (RIP-seq) to characterize RNA binding properties of repair proteins and chromatin complexes important in DNA repair should be a powerful approach to achieve this goal. Thestudy of ncRNA function in the cellular response to different types of DNA damage is still in its infancy. But it is already evident that ncRNAs are important players in maintaining genomic stability. Given the complexity suggested by the few identified players to date, it is likely that many additional DNA damage-relevant ncRNAs with various functions will be identified in the near future and will increase our understanding of mechanisms of maintaining genome stability.

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